IN THE SPECIFICATION:

Please amend the specification as follows.

Please add the following paragraph before "INTRODUCTION" on page 1 of the Application as filed:

CLAIM OF PRIORITY

The instant application is the U.S. national phase application of International application serial no. PCT/US99/06937, filed March 30, 1999, which application claims priority to U.S. provisional application serial no. 60/079,956, filed on March 30, 1998, and to U.S. provisional application serial no. 60/113,146, filed December 16, 1998, and to U.S. provisional application serial no. 60/113,146, filed December 16, 1998, all of which are incorporated herein by reference in their entirety.

Please replace the paragraph beginning at page 5, line 27, with the following:

The present invention further provides methods for identifying and designing molecules that modulate ligand binding to a nuclear receptor using atomic models of nuclear receptors. The method involves modeling test compounds that fit ~~specially~~ spatially into a nuclear receptor LBD using an atomic structural model comprising a nuclear receptor LBD or portion thereof, screening the test compounds in an assay, such as a biological assay, characterized by binding of a test compound to the nuclear receptor LBD, and identifying a test compound that modulates ligand binding to the receptor.

Please replace the paragraph beginning at page 10, line 26, with the following:

Certain residues within the ERα LBD have been identified that are of particular importance:Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528 (See Figure 4A). Of these, some have been found to directly or indirectly ~~effect~~ affect the positioning of helix 12: Met343, Met421, His524, Leu525 and Met528. Interactions with these particular residues, such as occurs when DES binds to the receptor stabilizes a conformation of the LBD that promotes coactivator binding. Modifications to a ligand that enhance binding or interaction with these residues would provide for an improved agonist of receptor activity. Similarly, modifications to a ligand that

adversely affects the binding or interaction with these residues would provide for an improved antagonist.

Please replace the paragraph beginning at page 16, line 10, with the following:

In particular, the present invention relates to the structural and functional effects on th estrogen receptor's LBD, of the binding of two chemically-related compounds, the agonist, diethylstilbestrol (DES), and the selective antagonist 4-hydroxytamoxifen (OHT), the active metabolite of tamoxifen. As described in the Examples, mutagenesis and binding studies, coupled with analysis of atomic models derived from cocrystals, reveals the structure of the human estrogen receptor α ligand binding domain (ERα LBD) co-crystallized with a peptide molecule comprising a GRIP1 NR Box II peptide sequence (SEQ ID NO:4) (i.e., a peptide derived from the NR Box II region of thc p160 coactivator GRIP1) bound to the coactivator binding site and the agonist, DES. Also revealed is the structure of the ERα LBD co-crystallized with the antagonist, OHT. The Examples provide the 2.03Å resolution crystal structure of the hERα LBD bound to DES and the coactivator and the 1.9Å x-ray crystal structure of the hERα LBD bound to OHT, i.e., the crystals ~~defract~~ diffract with at least 2.03Å or 1.9Å resolution, respectively.

Please replace the paragraph beginning at page 17, line 1, with the following:

Compounds of particular interest fit spatially and preferentially into the ligand binding domain. By "~~its~~ fits spatially and preferentially" is intended that a compound possesses a three-dimensional structure and conformation for selectively interacting with a nuclear receptor LBD. Compounds that fit spatially and preferentially into the LBD interact with amino acid residues forming the hydrophobic cleft of this site. The present invention also includes a method for identifying a compound capable of selectively modulating nuclear receptor activity. The method comprises the steps of modeling test compounds that fit spatially and preferentially into the LBD of a nuclear receptor of interest using an atomic structural model of a nuclear receptor, screening the test compounds in an assay for nuclear receptor activity characterized by preferential binding of a test compound to the LBD of a nuclear receptor, and identifying a test compound that selectively modulates the activity of a nuclear receptor. Such receptor-specific compounds are selected that exploit differences between the LBDs of one type of nuclear receptor versus a second type of nuclear receptor.

Please replace the paragraph beginning at page 18, line 29, with the following:

Chemical modifications will often enhance or reduce interactions between an atom of a LBD amino acid and an atom of [[an]] a LBD ligand. Steric hindrance will be a common means of changing the interaction of the LBD binding cavity with the activation domain. Chemical modifications are preferably introduced at C-H, C- and C-OH position in ligands, where the carbon is part of the ligand structure which remains the same after modification is complete. In the case of C-H, C could have 1, 2 or 3 hydrogens, but usually only one hydrogen will be replace. The H or OH are removed after modification is complete and replaced with the desired chemical moiety.

Please replace the paragraph beginning at page 29, line 25, with the following:

For co-crystallization with a ligand that binds the ligand binding domain, alone or in conjunction with a peptide that binds to the coactivator binding site, various concentrations of ligands and peptides containing a sequence that binds to a coactivator binding site of a nuclear receptor of interest can be used in microcrystallization trials, and the appropriate compounds selected for further crystallization. Ligands and peptides can be assayed for binding to the ligand binding domain and coactivator binding sites of a nuclear receptor of interest by any number of techniques, including those assays described herein. For crystallization trials with the ERα LBD, the hanging drop vapor diffusion method is preferred. Conditions of pH, solvent and solute components and concentrations and temperature can be adjusted, for instance, as described in the Examples. In the ~~handing~~ hanging drop method, to obtain suitable crystals for x-ray diffraction analysis, seeding of prepared drops with microcrystals of the complex can be used. Collection of structural information can be determined by molecular replacement using the structure of the ERα LBD determined herein. The structure is refined following standard techniques known in the art.